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Review of Myeloma Spotlights

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I would like to thank the UK Myeloma Forum for awarding me a bursary to attend the 62nd ASH annual meeting. This award gave a great opportunity to learn from leading international clinical experts and scientists on many management aspects for patients with multiple myeloma (MM). The award granted me an opportunity to present my work on real world outcomes in myeloma patients, during the poster presentation sessions; "Panobinostat in combination with Bortezomib and Dexamethasone for Heavily Pre-treated Myeloma: A UK Real-world multi-center Cohort".

I have recently started practicing as an independent prescriber managing myeloma patients; the programme offered an excellent learning platform; it was incredibly beneficial for my role in caring for myeloma patients to hear the new updates on various aspects of myeloma care including therapeutic approaches in the newly diagnosed setting, transplantation and in the relapsed setting, particularly the evolving role of CAR-T and other immunotherapies. Herein I provide a brief summary of studies from sessions I have attended reporting on treatment strategies in different stages in the disease course as presented by the main authors.

Smouledring MM

Treatment of High Risk (HR) Smoldering Multiple Myeloma (SMM) with Carfilzomib, Lenalidomide, and Dexamethasone (KRd) Followed By Lenalidomide Maintenance (-R): A Phase 2 Clinical and Correlative Study. By **Dickran Kazandjian**. *Session 653: Oral abstract, Paper ID: 548*

I have found this study particularly interesting, as it addressed the role of early intervention in asymptomatic smoldering patients at high risk of progression (HR-SMM), using a triplet based combination to achieving MRD negativity and reduce the risk of progression to symptomatic myeloma and therefore prolong survival. In this study; 52 patients with HR-SMM received 8 cycles of twice weekly carfilzomib 20/36 mg/m^{2}in combination with lenalidomide 25 mg days 1-21, and dexamethasone followed by 24 cycles of maintenance therapy with lenalidomide 10 mg. At 27.3 month follow up; MRD negative CR rate was 70.2% and the MRD negative ≥VGPR rate was 80.9%. The median time to progression to multiple myeloma was not reached. Grade 3/4 toxicities occurred in 33% of patients. Only 10% of patients developed multiple myeloma at 5-years compared to historical rates of 75% with no intervention.

Review comments: Other double and triplet combinations +/- maintenance +/- ASCT are being evaluated in smoldering myeloma. It would be interesting to see how these strategies translate into routine practice in the future and how best to optimize these interventions and balance maximum response with adverse events and risk of toxicities in asymptomatic patients.

Newly diagnosed MM

Daratumumab (DARA) Plus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Patients with Transplant-Eligible Newly Diagnosed Multiple Myeloma (NDMM): Updated Analysis of Griffin after 12 Months of Maintenance Therapy. By **Jonathan L. Kaufman**. *Session 653: Oral abstract, Paper ID: 549*

There is a shift in the management of newly diagnosed transplant-eligible myeloma patients towards newer treatment strategies employing a quadruplet-based induction incorporating an IMiD+PI+CD38 Mab, before high-dose therapy and ASCT, followed consolidation and maintenance. In this study; 207 patients were randomized to D-RVd (n=104) or RVd, (n=103). Patients received 4 induction cycles before high-dose therapy and ASCT, followed by 2 consolidation cycles, and maintenance with lenalidomide with or without DARA for 24 months. At post-transplant consolidation, with a median follow-up, 13.5 months, the sCR rate was higher in D-RVd group versus RVd (42.4% vs 32%). With the addition of lenaldiomide or lenalidomide plus DARA maintenance therapy, at the 12 months ofmaintenance therapy data cut, the median follow-up was 26.7 months, sCR and MRD negativity remained high in the D-RVd group 63.% and 62.5% respectively. The 24-month PFS rates were 94.5% and 90.8% for the D-RVd and RVd groups, respectively.

Review comments: In this study, maintenance therapy appears to further deepen responses with translated into prolonged progression free survival. High rates of grade 3/4 treatment-emergent adverse were reported in this study; 84.8% of patients in the D-RVd group and 79.4% in the RVd group. This study has highlighted the role of quadruplet induction and consolidation, followed by a doublet continuous therapy to achieve deep responses in transplant eligible patients. As we move towards these intensified treatment strategies in the future, careful patient selection is important in view of the associated significant treatment-related adverse events burden that will need to be managed carefully to optimize response and minimise toxicity.

Relapsed/Refractory MM

ANCHOR (OP-104): Melflufen Plus Dexamethasone (dex) and Daratumumab (dara) or Bortezomib (BTZ) in Relapsed/Refractory Multiple Myeloma (RRMM) Refractory to an IMiD and/or a Proteasome Inhibitor (PI) - Updated Efficacy and Safety. By **Enrique M. Ocio.** *Session 653: Oral, Paper ID: 417.*

This study evaluates new combinations incorporating a novel drug with a different mechanism of action; Melphalan flufenamide (melflufen) which is a first-in-class peptide-drug conjugate (PDC) that targets aminopeptidases and rapidly releases alkylating agents into tumor cells.

in this phase 1/2 study, varying doses of Melflufen 30, 40, or 20 mg was given intravenously in combination with Daratumumab or Bortezomib in patient with disease refractory to (or intolerant of) immunomodulatory agents and/or proteasome inhibitors, and who received 1-4 prior lines of therapy. Prior anti-CD38 mAb therapy was not permitted in patient assigned to the Daratumumab arm; patients in the BTZ arm could not have been PI-refractory. Melflufen was administered every 28-day cycle. Patients in both arms were treated until progressive disease or unacceptable toxicity. 33 patients received melflulen (30 mg, n=6; 40 mg, n=27) plus dexamethasone and daratumumab and 10 patients were treated with melflufen (30 mg, n=3; 40 mg, n=7) in combination with BTZ and dexamethasone.

In the Melflufen Dara Dex arm; the ORR was 70%. At a median follow-up of 11.9 months, the median PFS was 11.5 months. The most common grade 3/4 treatment-related adverse events were neutropenia (58%), thrombocytopenia (55%), and anaemia (24%). Twelve patients (36%) experienced serious treatment related adverse events most commonly influenza (9%), pneumonia, parainfluenza virus infection, and febrile neutropenia.

In the Melflufen BTZ Dex arm: ORR was 60%. PFS data was not mature. The most common grade 3/4 treatment related adverse events were thrombocytopenia (80%), neutropenia (60%), and anemia (40%). Six patients (60%) experienced serious TEAEs, most commonly pneumonia (20%).

Review comments: Melfulen offers a novel mechanism of action adding to the treatment armamentarium of relapsed multiple myeloma. Early data suggests activity; infections and G3/4 haematological toxicity were commonly reported in the combinations evaluated in this study. The optimal dose and combination requires further studies with longer follow up.

Immunotherapy in multiple myeloma

The field of immunotherapy in multiple myeloma is rapidly evolving with the introduction of CD38 monocloncal antibodies, CAR-T therapies, antibody-drug conjugates and bispecific and trispecific engager antibodies.

A number of studies were presented in highly refractory very difficult to treat patients including in penta-refractory disease. Novel modalities presented in the field of CAR-T therapies included: an allogeneic (off-the self) first in human study of anti-BCMA CAR-T therapy, newer fully human CAR-T products, and dual BCMA and CD19 targeted CAR-T Cell therapies.

I have attended a live Q&A session on immunotherapy in multiple myeloma. This session was very interesting. Topics covered and overview of immunotherapeutic targets in multiple myeloma. Speakers discussed the patient, tumor and prior treatment factors guiding treatment selection and sequencing with and after antibody therapies. Despite, CAR-T therapies inducing high and deep responses, relapse remains far too common, the panel considered how understanding the different mechanisms of relapse can help engineer potential CAR-T solutions. A comparison of the different immunotherapeutic approaches in terms of their advantages and challenges was debated.

Finally

I would like to thank again the UKMF for granting me this excellent opportunity; this was my first attendance at ASH, and I consider myself very lucky to have been able to be part of it in these very challenging times as we continue as a community to strive to improve outcomes for our haematology patients.